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How Sensitive Are Epidermal Growth Factor Receptor–Tyrosine Kinase Inhibitors for Squamous Cell Carcinoma of the Lung Harboring EGFR Gene–Sensitive Mutations?

In Response:

We are thankful for the thoughtful suggestions by Zhou et al.[1] They raised two intriguing questions: first, which is better, platinum doublets or epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitor (TKI) as first-line treatment in squamous cell carcinoma (SQC) patients with EGFR-sensitive mutations; and second, how do we treat patients with minor EGFR mutations?

Several studies in patients with *EGFR* mutations demonstrated the efficacy of platinum doublets; and the response rate (RR) and median progression-free survival (PFS) were approximately 30% and 6 months,[2] similar to our 14 *EGFR*-mutated SQC patients receiving platinum doublets as first-line treatment. Compared with our EGFR-TKI results (RR, 25% and median PFS, 1.4 months),[3] we would generally choose platinum doublets as first-line treatment before EGFR-TKIs in such patients. However, we should ponder how many *EGFR*-mutated adenocarcinoma cells are included in an SQC case. If the *EGFR*-mutated SQC patient is suspected as harboring *EGFR*-mutated adenocarcinoma propensity per the following factors: female, never smoker, high carcinoembryonic antigen, and thyroid transcription factor-1 positive, we could try EGFR-TKI as a first-line treatment. Conversely, male, current smoker, high cytokeratin 19 fragment, and p63 positive patients would be better served by platinum doublets. We should recognize some *EGFR*-mutated SQC include an incomplete sampling of adeno-SQC and/or poorly differentiated adenocarcinoma morphologically mimicking SQC. Approximately one third of the *EGFR*-mutated SQC patients in our study obtained a PFSof longer than 6 months, and most of them had adenocarcinoma propensities. To better identify EGFR-TKI–sensitive SQC patients, not only *EGFR* mutation status, but also clinical factors and pathologic findings should be taken into consideration.

Unfortunately, both of our two patients with a G719X point mutation in exon 18 did not undergo EGFR-TKIs in our study. Sensitivities of EGFR-TKIs in minor *EGFR* mutations such as G719X seem to be less effective than major mutations such as deletional mutations in exon 19 and a L858R point mutation in exon 21. In patients with minor mutations, the RR and PFS were shown to be 30% to 50% and 3 to 5 months, comparable to platinum doublets.[4] In our opinion, we would choose platinum doublets as first-line treatment, before EGFR-TKI in patients with minor mutations. It is more difficult to administer platinum doublets as second-line treatment, compared with EGFR-TKI. In patients with SQC harboring minor mutations, priority of EGFR-TKI becomes much lower.

The diagnostic limitations of small biopsies and intratumoral heterogeneity make definitive diagnoses difficult.[5] Clinicians should understand the limitations of pathologic diagnosis based on small biopsies, and need to cooperate with pathologists to better reach a diagnosis for individual patients. EGFR-TKI sensitivity in *EGFR*-mutated SQC should be judged by the general factors of the patient.

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